Occupational Exposures and Computed Tomographic Imaging Characteristics in the SPIROMICS Cohort

Laura M. Paulin[1], Benjamin M. Smith[2,3], Abby Koch[4], MeiLan Han[5], Eric A. Hoffman[6], Carlos Martinez[5], Chinedu Ejike[5], Paul D. Blanc[7], Jennifer Rous[8], R. Graham Barr[2], Stephen P. Peters[9], Robert Paine III[10], Cheryl Pirozzi[10], Christopher B. Cooper[11], Mark T. Dransfield[12], Alejandro P. Comellas[13], Richard E. Kanner[10], M. Brad Drummond[14], Nirupama Putcha[4], and Nadia N. Hansel[4]

[1]Department of Medicine, Dartmouth-Hitchcock Medical Center/Geisel School of Medicine at Dartmouth, Lebanon, New Hampshire; [2]Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, New York; [3]Translational Research in Respiratory Diseases Program, Department of Medicine, McGill University Health Centre Research Institute, Montreal, Quebec, Canada; [4]Department of Medicine, Johns Hopkins University, Baltimore, Maryland; [5]Department of Medicine, University of Michigan, Ann Arbor, Michigan; [6]Department of Radiology, University of Iowa, Iowa City, Iowa; [7]Department of Medicine, University of California, San Francisco, San Francisco, California; [8]Department of Environmental Health and Engineering, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; [9]Department of Medicine, Wake Forest University, Winston-Salem, North Carolina; [10]Department of Medicine, University of Utah, Salt Lake City, Utah; [11]Department of Medicine, University of California, Los Angeles, Los Angeles, California; [12]Department of Medicine, University of Alabama, Birmingham, Alabama; [13]Department of Medicine, University of Iowa, Iowa City, Iowa; and [14]Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

ORCID IDs: 0000-0003-1521-7520 (A.P.C.); 0000-0002-6968-4610 (M.B.D.).

Abstract

Rationale: Quantitative computed tomographic (CT) imaging can aid in chronic obstructive pulmonary disease (COPD) phenotyping. Few studies have identified whether occupational exposures are associated with distinct CT imaging characteristics.

Objectives: To examine the association between occupational exposures and CT-measured patterns of disease in the SPIROMICS (Subpopulations and Intermediate Outcome Measures in COPD Study).

Methods: Participants underwent whole-lung multidetector helical CT at full inspiration and expiration. The association between occupational exposures (self-report of exposure to vapors, gas, dust, or fumes [VGDF] at the longest job) and CT metrics of emphysema (percentage of total voxels < -950 Hounsfield units at total lung capacity), large airways (wall area percent [WAP] and square-root wall area of a single hypothetical airway with an internal perimeter of 10 mm [Pi10]), and small airways (percent air trapping [percent total voxels < -856 Hounsfield units at residual volume] and parametric response mapping of functional small-airway abnormality [PRM fSAD]) were explored by multivariate linear regression, and for central airway measures by generalized estimating equations to account for multiple measurements per individual. Models were adjusted for age, sex, race, current smoking status, pack-years of smoking, body mass index, and site. Airway measurements were additionally adjusted for total lung volume.

Results: A total of 2,736 participants with available occupational exposure data ($n = 927$ without airflow obstruction and 1,809 with COPD) were included. The mean age was 64 years, 78% were white, and 54% were male. Forty percent reported current smoking, and mean (SD) pack-years was 49.3 (26.9). Mean (SD) post-bronchodilator forced expiratory volume in 1 second (FEV_1) was 73 (27) % predicted. Forty-nine percent reported VGDF exposure. VGDF exposure was associated with higher emphysema ($\beta = 1.17$; 95% confidence interval [CI], 0.44–1.89), greater large-airway disease as measured by WAP (segmental $\beta = 0.487$ [95% CI, 0.320–0.654]; subsegmental $\beta = 0.400$ [95% CI, 0.275–0.527]) and Pi10 ($\beta = 0.008$; 95% CI, 0.002–0.014), and greater small-airway disease was measured by air trapping ($\beta = 2.60$; 95% CI, 1.11–4.09) and was nominally associated with an increase in PRM fSAD ($\beta = 1.45$; 95% CI, 0.31–2.60). These findings correspond to higher odds of percent emphysema, WAP, and air trapping above the 95th percentile of measurements in nonsmoking control subjects in individuals reporting VGDF exposure.

Conclusions: In an analysis of SPIROMICS participants, we found that VGDF exposure in the longest job was associated with an increase in emphysema, and in large- and small-airway disease, as measured by quantitative CT imaging.

Keywords: chronic obstructive pulmonary disease; outcome assessment; quantitative computed tomography

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Chronic obstructive pulmonary (COPD) is a leading cause of death and morbidity worldwide (1). Development of COPD is the result of long-term exposure to inhaled noxious gases and particles, including not only cigarette smoke but also dusts, fumes, and vapors found in work environments. The relationship between occupational exposures and the development of COPD is now well recognized, even when accounting for cigarette smoking (2, 3), and among those with established COPD, those with occupational exposures have worse morbidity and disease severity (4–8).

COPD is a disease encompassing varying airway and alveolar abnormalities, and research has utilized quantitative computed tomographic (CT) imaging as a tool to aid in differentiating distinct COPD phenotypes based on radiologic patterns, including emphysema, large-airway abnormalities, and small-airway disease (9–11). These distinct CT phenotypes are associated with varying clinical presentations of disease; however, there are few published data on how environmental exposures, and more specifically, occupational exposures, may influence these CT-measured characteristics (12–15). This work aims to further clarify the association between occupational exposures and CT-measured patterns of disease in the SPIROMICS (Subpopulations and Intermediate Outcome Measures in COPD Study) cohort, a multicenter prospective cohort study aiming to identify new COPD subgroups and intermediate markers of disease progression that predict long-term clinical endpoints of morbidity (16). We hypothesize that occupational exposures are associated with a greater burden of CT-measured parenchymal and airway disease among former and current smokers enrolled in the SPIROMICS cohort. Some of the results of this study have been previously reported in the form of an abstract (17).

Methods

Study Population

The SPIROMICS cohort includes current and former smokers with and without airway obstruction. Individuals aged 40–80 years old with at least a 20–pack-year smoking history were enrolled in SPIROMICS at six clinical sites and subsites across the United States. Participants were recruited from the population at each center by means of physician referral, advertisement in clinical areas, or self-referral at the study website (www.spiromics.org). Those defined as having COPD had a post-bronchodilator FEV_1/FVC ratio less than 0.70. Smokers without COPD had a post-bronchodilator FEV_1/FVC greater than 0.70 and an FVC greater than the lower limit of normal. A smaller group of nonsmoking control subjects was recruited into SPIROMICS; results from this group were used to obtain abnormal cutoffs for CT-measured outcomes only and were not otherwise included in this analysis. Exclusion criteria included a diagnosis of other obstructive lung diseases besides asthma, body mass index (BMI) greater than 40 kg/m^2, history of lung cancer, and diagnosis of unstable cardiovascular disease. The study and additional exclusion criteria have been previously described (16).

At the baseline visit, trained staff collected extensive demographic and clinical data from participants, including respiratory-specific quality of life (St. George's Respiratory Questionnaire) (18), exercise capacity (6-min walk distance, in meters) (19), dyspnea (modified Medical Research Council questionnaire) (20), and COPD health status (COPD Assessment Test) (21). Smoking history was determined by current smoking status, defined as whether the participant reporting smoking within the last month, and lifetime cumulative pack-years of smoking. Spirometry was performed according to standard procedure (22, 23). The current study is a cross-sectional analysis of baseline data from 2,736 participants with available occupational exposure data ($n = 927$ smokers without airway obstruction and 1,809 smokers with COPD). SPIROMICS was approved by institutional review boards at each center, and all participants provided written informed consent.

Exposure Assessment

Occupational history was obtained using an interviewer-administered semistructured questionnaire. Participants were queried on occupational history and details about current and former jobs. The primary exposure variable used in this analysis was report of exposure to vapors, gas, dust, or fumes (VGDF) at the longest job, which was ascertained by the widely used yes/no question: "Did this job expose you to vapors, gas, dust, or fumes?" (24–26).

Quantitative CT Measures

Participants underwent whole-lung multidetector helical CT at full inspiration and expiration as previously described (10). The primary outcomes were CT measures of airway structure and parenchymal characteristics, including the following:

1. Emphysema as measured by percent emphysema, defined as percentage of total voxels in the field less than −950 Hounsfield units at total lung capacity.
2. Large-airway disease as identified using airway dimensions including area and diameter of walls and lumens of spatially matched segmental and subsegmental

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Correspondence and requests for reprints should be addressed to Laura M. Paulin, M.D., M.H.S., Dartmouth-Hitchcock Medical Center, 1 Medical Center Drive, Pulmonary 5C Suite, Lebanon, NH 03756. E-mail: laura.m.paulin@hitchcock.org.

airways, using techniques as previously described (9). Values of wall area, lumen area, and wall area percent (WAP), a measure of airway wall thickness relative to total airway size, were obtained from measured dimensions. In addition, Pi10, a measure of airway wall thickness, was calculated by regressing the square-root wall area on the internal perimeter of included airways to predict the square-root wall area of a single hypothetical airway with internal perimeter of 10 mm.

3. Small-airway disease as measured by percent gas trapping, defined as the percentage of total voxels in the field less than −856 Hounsfield units at residual volume, and parametric response mapping of functional small-airway abnormality (PRM fSAD). PRM provides analysis of paired inspiratory and expiratory CTs to identify and quantify the extent of small-airway abnormalities, using the Imbio Lung Density Analysis software application as previously described (Imbio, LLC) (11). The extent of PRM fSAD is described as a percentage of the whole lung area.

Statistical Analysis

Descriptive statistics of participants reporting VGDF exposure in the longest job were compared with those who did not report such exposures, using χ^2 tests for proportions and *t* tests or Wilcoxon-Mann-Whitney tests for continuous data, as appropriate. In all current and former smokers, multivariable linear regression models were used to examine the cross-sectional association between occupational exposures in the longest job and CT metrics of Pi10, percent emphysema, percent gas trapping, and PRM fSAD. In addition to modeling CT imaging outcomes as continuous variables, logistic regression was used to determine the cross-sectional association between VGDF exposure and imaging values above the 95th percentile value in nonsmoking control subjects (emphysema, 4.5%; Pi10, 3.8 mm; WAP, 65.0% [segmental], 68.5% [subsegmental]; gas trapping, 21.6%; PRM fSAD, 24.4%; *see* Table 2), as previously done in a large study of occupational exposures in COPD (12). Models were adjusted for age, sex, race (white vs. nonwhite), body mass index (BMI; underweight, <18.5 kg/m^2; normal weight, 18.5 to <25 kg/m^2; overweight, 25 to <30 kg/m^2; obese, at least 30 kg/m^2), study site, current smoking status, and pack-years of smoking. For the analyses of central airway dimensions (wall area, lumen area, and wall area percent), generalized estimating equations were used to account for multiple measurements per participant, controlling for the same factors as listed above in addition to total lung volume achieved at CT (9).

In a sensitivity analysis, to explore whether the relationship between VGDF exposure and CT phenotype was similar in those with COPD, analyses were limited to the individuals with spirometry-confirmed airway obstruction. To address the role of socioeconomic status, additional analysis included participant education (greater or less than high school education) as a covariate. To determine whether smoking status modified susceptibility to VGDF exposure, interaction terms between current smoking status and pack-years with VGDF exposure were created separately. Effect modification by sex was also explored. All analyses were performed with StataMP statistical software, version 12.1 (StataCorp). Given that multiple CT outcomes were tested (10 in total), the Bonferroni correction was utilized to set the threshold for statistical significance at 0.005. $\alpha = 0.1$ was the threshold for interaction terms (27).

Results

Participant Characteristics

Current or former smokers (2,736) with available occupational exposure data were included in the analysis. The majority of participants were white, had a mean age of 64 years, and 54% were male. Forty percent reported current smoking, and mean (SD) pack-years reported was 49.3 (26.9). Mean post-bronchodilator FEV_1 was 73.1 (26.5) % predicted. Of the participants, 49.2% reported VGDF exposure in their longest job, and those reporting VGDF exposure tended to be younger, male, and nonwhite; to have lower FEV_1 percent predicted; and to have higher modified Medical Research Council questionnaire, COPD Assessment Test, and St. George's Respiratory Questionnaire scores than individuals not reporting exposure to VGDF in their longest job. Smoking patterns did not differ between those reporting and those not reporting VGDF (Table 1). Of note, these comparisons between those with and without job exposures are similar to data that were previously published with a smaller sample size of the same cohort (4).

CT Characteristics

Emphysema. Participants reporting exposure to VGDF in their longest job had greater emphysema (Table 2). Of the participants, 42.7% had an emphysema percentage above the 95th percentile of nonsmoking control subjects. In bivariate analysis of current and former smokers, VGDF exposure in the longest job was associated with a 1.11% greater amount of emphysema ($P < 0.005$). After adjustment for confounders, report of VGDF exposure in the longest job continued to be associated with greater emphysema (1.17% increase; $P = 0.002$) (Table 3). This corresponds to 34% increased odds (odds ratio [OR], 1.34; 95% confidence interval [95% CI], 1.12–1.60) of having percent emphysema greater than 95% of nonsmoking control subjects (e.g., more than 4.5% emphysema). Inclusion of education in the model did not meaningfully alter these results. There was no evidence of effect modification by pack-years of smoking or smoking status (current vs. former) on the relationship between VGDF exposure and emphysema. There was no statistically significant interaction between sex and VGDF exposure, although the impact of VGDF on emphysema tended to be greater in men versus women (Table 4).

Large-airway disease. Participants reporting exposure to VGDF in the longest job had greater WAP in the segmental and subsegmental airways and greater Pi10 compared with those without job exposures (Table 2). Of the participants, 11.7% had a Pi10 value greater than the 95th percentile value in nonsmoking control subjects. Of the segmental and subsegmental airways, 16.3 and 15.3%, respectively, were greater than the 95th percentile of values found in nonsmoking control subjects. In bivariate analysis of current and former smokers, VGDF exposure in the longest job was associated with a higher WAP (segmental airways: $\beta = 0.475$, $P < 0.001$; subsegmental airways: $\beta = 0.346$, $P < 0.001$). After adjustment for confounders, report of VGDF exposure continued to be associated with a higher WAP: 0.457% higher in segmental and 0.400% higher in subsegmental airways ($P < 0.001$ for both) (Table 3). These correspond to 19% increased odds (OR, 1.19; 95% CI,

Table 1. Baseline participant characteristics by report of exposure to vapors, gas, dust, or fumes in longest job

	Current or Former Smokers (Stratum 2–4) (*N* = 2,736)		
	All Participants	**No VGDF Exposure in Longest Job (*n* = 1,390)**	**VGDF Exposure in Longest Job (*n* = 1,346)**
Age, mean (SD), yr	63.5 (8.9)	64.9 (8.8)	62.1 (8.8)
Sex, male, *n* (%)	1,487 (54.3)	616 (44.3)	871 (64.7)
Race, white, *n* (%)	2,100 (76.8)	1,096 (78.8)	1,004 (74.6)
BMI, mean (SD), kg/m^2	27.9 (5.3)	27.7 (5.3)	28.2 (5.3)
Pack-years, mean (SD)	49.3 (26.9)	48.7 (28.3)	50.0 (25.5)
Current smoker, *n* (%)	1,093 (40.0)	531 (38.2)	540 (40.1)
Years at longest job, mean (SD)	22.3 (12.1)	21.7 (12.2)	23.0 (12.0)
Currently working, *n* (%)	734 (26.8)	357 (25.7)	377 (28.0)
COPD diagnosis, *n* (%)	1,809 (66.1)	895 (64.4)	914 (67.9)
Post-BD FEV_1% pred, mean (SD)	73.1 (26.5)	75.6 (26.0)	70.4 (26.6)
Six-minute walk test distance, mean (SD), m	407.7 (120.6)	409.6 (121.1)	405.8 (120.6)
mMRC score, mean (SD)	1.08 (1.0)	1.01 (0.97)	1.15 (1.03)
CAT score, mean (SD)	14.1 (8.3)	13.1 (7.9)	15.2 (8.4)
SGRQ score, mean (SD)	33.6 (20.6)	30.7 (19.9)	36.4 (20.7)

Definition of abbreviations: BD = bronchodilator; BMI = body mass index; CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; mMRC = modified Medical Research Council questionnaire; SD = standard deviation; SGRQ = St. George's Respiratory Questionnaire; VGDF = vapors, gas, dust, or fumes.

1.07–1.32) in segmental airways and 11% increased odds (OR, 1.11; 95% CI, 1.01–1.22) in subsegmental airways of having a WAP greater than the 95th percentile of nonsmoking control subjects. This appeared to be driven primarily by a relatively smaller airway lumen area as compared with airway wall area. VGDF exposure was also nominally associated with a marginally higher Pi10 (unadjusted: β coefficient = 0.011 mm, $P < 0.001$; adjusted: β coefficient = 0.008 mm, $P = 0.01$). Accounting for education in the model did not meaningfully alter results.

When exploring effect modification by smoking status, a significant interaction was found between current smoking status and VGDF exposure for wall area percent (segmental *P*-int = 0.04; subsegmental *P*-int = 0.002), such that exposure to VGDF in the longest job had a larger impact on large airways among former compared with current smokers. Specifically, VDGF exposures was associated with 0.605 and 0.538 higher segmental and subsegmental WAP (95% CI, 0.387–0.824, 95% CI, 0.372–0.703, respectively; $P < 0.001$ for both) in former smokers and a 0.314 and 0.213 higher segmental and subsegmental WAP (95% CI, 0.053–0.576, $P = 0.02$; 95% CI, 0.015–0.410, $P = 0.04$), respectively, in current smokers. There was no evidence of effect modification by smoking status for Pi10, and there was no significant interaction between pack-years of smoking and any of the large-airway outcomes.

When exploring effect modification by sex, there was no statistically significant interaction between VGDF exposure and sex for Pi10, although in stratified analysis, VGDF exposure was associated with a greater Pi10 in men than women (0.011 mm, $P = 0.02$ in men; 0.004, $P = 0.32$ in women). The association between VGDF exposure and airway lumen area and WAP in the segmental airways was greater in men than women (−0.968, $P = 0.003$ in men; −0.245, $P = 0.30$ in women; *P*-int = 0.09) (0.681, $P < 0.001$ in men; 0.324, $P = 0.01$ for women; *P*-int = 0.10), respectively (Table 4).

Small-airway disease. Of the participants, 44.3% and 38.3% had values of gas trapping and PRM fSAD greater than the 95th percentile of nonsmoking control subjects, respectively. There was no statistically significant difference in gas trapping or PRM fSAD between groups with and without occupational exposures (Table 2); however, in bivariate analysis of current and former smokers, VGDF exposure was nominally associated with higher percent gas trapping (β coefficient = 1.53; $P = 0.07$). After adjustment for confounders, report of VGDF exposure became significantly associated with 2.60% higher gas trapping ($P = 0.001$), which corresponds to an OR of 1.25 (1.05–1.49) of having gas trapping greater than 21.6%. There was a continued nominal association with 1.45% higher PRM fSAD ($P = 0.01$) (Table 3), corresponding with an OR of 1.16 (0.96–1.39) for greater than 24.4% PRM fSAD. Including education as a covariate did not meaningfully alter these relationships. There was no evidence of effect modification by pack-years of smoking or by smoking status (current vs. former) on the relationship between VGDF exposure and gas trapping or PRM fSAD. Although not a statistically significant interaction, the effect of VGDF exposure on small airways tended to be greater in men versus women in stratified analysis (Table 4).

Effect of VGDF on CT Outcomes in Individuals with Airflow Obstruction ($FEV_1/FVC < 0.70$)

When limited to those individuals with spirometry-confirmed COPD ($n = 1,809$), the relationship between VGDF exposure and a greater amount of large-airway disease as measured by wall area percent remained statistically significant. The association between VGDF exposure and emphysema had similar directions of effect, but this association was no longer statistically significant. The relationship between VGDF exposure and CT-measured small-airway disease was slightly attenuated in individuals with COPD and reached nominal statistical significance (Table 5).

Discussion

In this study of current and former smokers enrolled in the SPIROMICS cohort, the

Table 2. Quantitative computed tomographic characteristics by report of exposure to vapors, gas, dust, or fumes in longest job

	Nonsmoking Control Subjects (*n = 202*)	Current and Former Smokers (*n = 2,736*)	Current and Former Smokers without VGDF Exposure in Longest Job (*n = 1,390*)	Current and Former Smokers with VGDF Exposure in Longest Job (*n = 1,346*)	*P* Value
Emphysema					
% emphysema, median (IQR)	1.0 (1.4)	3.2 (9.8)	**2.9 (8.7)**	**3.5 (11.2)**	**0.002**
% emphysema, 95th percentile	4.5				
Large airway					
Pi10, mean (SD), mm	3.67 (0.08)	3.71 (0.08)	**3.71 (0.08)**	**3.72 (0.08)**	**<0.001**
Pi10, 95th percentile	3.80				
Wall area %, mean (SD)					
Segmental	57.5 (4.1)	60.6 (4.7)	**60.4 (4.8)**	**60.8 (4.7)**	**<0.001**
Subsegmental	61.4 (3.8)	64.1 (4.6)	64.0 (4.8)	64.1 (4.5)	0.06
Wall area %, 95th percentile					
Segmental	65.0				
Subsegmental	68.5				
Airway lumen area, median (IQR), mm^2					
Segmental	24.5 (10.8)	20.4 (11.6)	**20.0 (11.4)**	**20.7 (11.6)**	**<0.001**
Subsegmental	14.5 (6.4)	11.1 (7.9)	**11.0 (7.8)**	**11.3 (8.1)**	**0.002**
Airway wall area, mean (SD), mm^2					
Segmental	37.8 (8.9)	32.8 (9.9)	**32.1 (9.6)**	**33.6 (10.1)**	**<0.001**
Subsegmental	26.1 (8.4)	21.7 (9.1)	**21.4 (9.3)**	**22.0 (8.8)**	**<0.001**
Small airway					
% gas trapping, median (IQR)	3.4 (7.1)	18.3 (33.2)	17.9 (31.9)	18.7 (34.8)	0.10
% gas trapping, 95th percentile	21.6				
% PRM fSAD, median (IQR)	3.8 (8.0)	18.1 (25.0)	17.6 (24.8)	18.3 (25.1)	0.38
% PRM fSAD, 95th percentile	24.4				

Definition of abbreviations: IQR = interquartile range; Pi10 = estimated square-root wall area of a single hypothetical airway with internal perimeter of 10 mm; PRM fSAD = parametric response mapping of functional small-airway abnormality; SD = standard deviation; VGDF = vapors, gas, dust, or fumes.
Boldface entries indicate a statistically significant association with $P < 0.005$.

effect of occupational exposure on three distinct CT phenotypes was evaluated. Exposure to VDGF in the longest job was associated with a greater degree of three measured patterns on CT imaging, all of which are associated with important clinical outcomes, including increased exacerbations (28), worse quality of life (29), and impairment in lung function (9, 30, 31). In addition, for the majority of outcomes, participants with VGDF exposure had higher odds of having CT measurements of greater than the 95th percentile of nonsmoking SPIROMICS control subjects, further demonstrating a higher burden of CT-measured patterns of disease in an occupationally exposed population. The results of this study offer insight into the potential pathways responsible for the worse outcomes observed in occupationally exposed individuals.

This study adds to the limited body of knowledge that describes the relationship between occupational exposures and variations in CT phenotype. In a small study of 29 workers exposed to World Trade Center disaster dust, longer duration of dust exposure was associated with greater CT-measured air trapping. The authors suggest that the small-airway dysfunction represented by the greater degree of air trapping may account for some of the clinical abnormalities reported in this cohort (32). In a general population study of 1,050 Swedes, Torén and colleagues report a significant association between occupational exposure to VGDF and emphysema (as visually assessed by a radiologist) (OR, 1.8; 95% CI, 1.1–3.1) (14). Our study supports these findings using a quantitative definition of emphysema. In a cross-sectional analysis of CT phenotype in a population of current and former smokers with and without airway obstruction in COPDGene, Marchetti and colleagues found that occupational exposures were associated with a burden of percent emphysema and air trapping similar to the degree found in SPIROMICS. Self-reported exposure to dust and fumes at any point in the occupational history was associated with more emphysema and air trapping, even when considering pack-years of smoking and current smoking status (12).

The addition of PRM fSAD measurements further strengthens the evidence that occupational exposures are associated with a greater degree of small-airway disease in current and former smokers. PRM fSAD is thought to have additional value over percent gas trapping (based on the <-856 Hounsfield units method) as the matching of inspiratory and expiratory scans at each voxel helps to distinguish between nonemphysematous and emphysematous gas trapping and more precisely quantifies gas trapping (11, 33). In a previous study done in SPIROMICS, PRM fSAD was associated with a decreased FEV_1/FVC ratio (11), and in a study of current and former smokers in the COPDGene cohort, Bhatt and colleagues report an association between PRM fSAD and decline in FEV_1 throughout Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages (30), suggesting that this measurement is a marker of clinically meaningful outcomes. To our knowledge, this is the first study

Table 3. Relationship between vapors, gas, dust, or fumes exposure in the longest job and computed tomographic measures of airway remodeling and lung parenchyma in current and former smokers

Current and Former Smokers (*n* = 2,736)	Longest Job Exposure			Longest Job Exposure (Adjusted for Age, Sex, Race, Current Smoking Status, Pack-Years of Smoking, BMI, Study Site)		
	β	CI	*P* Value	β	CI	*P* Value
Emphysema						
% emphysema	1.11	0.33 to 1.89	0.01	**1.17**	**0.44 to 1.89**	**0.002**
Large airway						
Pi10 (whole lung)	**0.011**	**0.005 to 0.017**	**<0.001**	0.008	0.002 to 0.014	0.01
Wall area %*						
Segmental	**0.475**	**0.312 to 0.637**	**<0.001**	**0.487**	**0.320 to 0.654**	**<0.001**
Subsegmental	**0.346**	**0.223 to 0.468**	**<0.001**	**0.400**	**0.275 to 0.527**	**<0.001**
Airway lumen area*						
Segmental	−0.107	−0.505 to 0.291	0.60	**−0.652**	**−1.060 to −0.244**	**0.002**
Subsegmental	−0.577	−1.226 to 0.071	0.08	−0.846	−1.521 to −0.170	0.01
Airway wall area*						
Segmental	**0.618**	**0.291 to 0.944**	**<0.001**	−0.156	−0.481 to 0.169	0.35
Subsegmental	0.058	−0.189 to 0.306	0.64	−0.297	−0.549 to −0.045	0.02
Small airway						
% air trapping	1.53	−0.11 to 3.16	0.07	**2.6**	**1.11 to 4.09**	**0.001**
% PRM fSAD	0.41	−0.81 to 1.64	0.51	1.45	0.31 to 2.60	0.01

Definition of abbreviations: BMI = body mass index; CI = confidence interval; Pi10 = estimated square-root wall area of a single hypothetical airway with internal perimeter of 10 mm; PRM fSAD = parametric response mapping of functional small-airway abnormality.
*Additionally adjusted for lung volume.
Boldface entries indicate a statistically significant association with $P < 0.005$.

to examine the relationship between VGDF exposure and small-airway abnormalities as measured by PRM fSAD, and supports the link between VGDF exposure and small-airway disease as measured by gas trapping.

Few studies have explored the relationship between occupational exposures and large-airway disease. Lai and colleagues explored the relationship between occupational endotoxin exposure and CT phenotype in a cohort of 464 Taiwanese

Table 4. Relationship between vapors, gas, dust, or fumes exposure in the longest job and computed tomographic measures of airway remodeling and lung parenchyma in current and former smokers stratified by sex

Current and Former Smokers (*n* = 2,736)	Longest Job Exposure (Adjusted for Age, Sex, Race, Current Smoking Status, Pack-Years of Smoking, BMI, Study Site)						*P*-Int
	Men (*n* = 1,487)			Women (*n* = 1,249)			
	β	95% CI	*P* Value	β	95% CI	*P* Value	
Emphysema							
% emphysema	1.32	0.29 to 2.35	0.01	0.97	−0.06 to 1.99	0.07	0.93
Large airway							
Pi10 (whole lung)	0.011	0.002 to 0.020	0.02	0.004	−0.004 to 0.013	0.32	0.54
Wall area %*							
Segmental	**0.681**	**0.448 to 0.914**	**<0.001**	0.324	0.787 to 0.569	0.01	0.10
Subsegmental	**0.541**	**0.372 to 0.710**	**<0.001**	0.233	0.409 to 0.425	0.02	0.16
Airway lumen area*							
Segmental	**−0.968**	**−1.610 to −0.324**	**0.003**	−0.245	−0.712 to 0.220	0.30	0.09
Subsegmental	−1.362	−2.563 to −0.161	0.03	−0.225	−0.548 to 0.098	0.17	0.16
Airway wall area*							
Segmental	−0.277	−0.784 to 0.230	0.28	0.110	−0.282 to 0.502	0.58	0.15
Subsegmental	−0.449	−0.876 to −0.061	0.02	−0.059	−0.362 to 0.245	0.71	0.19
Small airway							
% air trapping	**3.07**	**0.98 to 5.17**	**0.004**	1.66	−0.48 to 3.81	0.13	0.66
% PRM fSAD	1.71	0.14 to 3.28	0.13	0.70	−0.99 to 2.39	0.42	0.64

Definition of abbreviations: BMI = body mass index; CI = confidence interval; Pi10 = estimated square-root wall area of a single hypothetical airway with internal perimeter of 10 mm; *P*-int = *P* value of the interaction term; PRM fSAD = parametric response mapping of functional small-airway abnormality.
*Additionally adjusted for lung volume.
Boldface entries indicate a statistically significant association with $P < 0.005$.

Table 5. Relationship between vapors, gas, dust, or fumes exposure in the longest job and computed tomographic measures of airway remodeling and lung parenchyma in spirometry-confirmed chronic obstructive pulmonary disease

Spirometry-confirmed COPD (*n = 1,809*)	Longest Job Exposure (Adjusted for Age, Sex, Race, Current Smoking Status, Pack-Years of Smoking, BMI, Study Site)		
	β	CI	*P* value
Emphysema			
% emphysema	0.76	−0.21 to 1.74	0.12
Large airway			
Pi10 (whole lung)	0.003	−0.005 to 0.011	0.43
Wall area %*			
Segmental	**0.302**	**0.098 to 0.506**	**0.004**
Subsegmental	**0.321**	**0.164 to 0.479**	**<0.001**
Airway lumen area*			
Segmental	−0.379	−0.875 to 0.118	0.14
Subsegmental	−1.025	−2.087 to 0.037	0.06
Airway wall area*			
Segmental	−0.062	−0.409 to 0.397	0.98
Subsegmental	−0.371	−0.704 to −0.038	0.03
Small airway			
% air trapping	2.05	0.23 to 3.87	0.03
% PRM fSAD	1.32	−0.02 to 2.67	0.05

Definition of abbreviations: BMI = body mass index; CI = confidence interval; COPD = chronic obstructive pulmonary disease; Pi10 = estimated square-root wall area of a single hypothetical airway with internal perimeter of 10 mm; PRM fSAD = parametric response mapping of functional small-airway abnormality.
*Additionally adjusted for lung volume.
Boldface entries indicate a statistically significant association with $P < 0.005$.

fabric workers. In the study, occupational exposure to endotoxin was associated with a 2.3% increase in wall area percent with no significant interaction between occupational exposures and smoking exposure (pack-years of smoking and current smoking status) for CT phenotypes (13). Marchetti and colleagues found that men reporting exposure to dust and fumes, but not women, had greater Pi10 (12). Although the interaction for Pi10 as an outcome was not significant in our analyses, there was a trend toward a greater effect of VGDF exposure on Pi10 in men versus women; moreover, the effect of VGDF exposure on WAP was greater in men than women, suggesting that the large-airway response to VGDF exposure may vary by sex. Why men may be more susceptible to VDGF exposure remains unknown, but may be explained by physiological differences (34–36), including larger airway size (37), which may result in less ability for airway defense mechanisms to clear noxious materials. Further, actual exposures may vary between job duties even within the same occupation (38), which would not be captured by the VGDF exposure variable.

The current study supports this work in that VGDF exposure was associated with an increase in WAP, and provides further insight into this relationship with the availability of spatially matched airways, avoiding potential selection bias of airways in the lung. This association was driven mainly by VDGF being associated with smaller airway lumen areas, more so than changes in wall area, resulting in higher WAP. A pattern of higher WAP due to smaller lumen areas has been reported in prior studies of individuals with COPD (9), but to our knowledge has not been previously observed in association with occupational exposures. In a prior analysis of SPIROMICS data, WAP was significantly greater in those with spirometry-diagnosed COPD, and higher WAP was associated with worse lung function (9). In COPDGene, higher WAP was associated with a clinical phenotype of chronic bronchitis (39). This is not unexpected as patients with chronic bronchitis have previously been shown, pathologically, to have more airway inflammation, primarily affecting the larger airways as opposed to the smaller or more peripheral airways (40). In addition, individuals with chronic bronchitis have more symptoms and exacerbations (41), suggesting that WAP may be a useful marker of worse COPD morbidity.

In contrast to the study by Lai and colleagues, the current study found that VDGF exposure had nearly double the effect size in former smokers as compared with current smokers for the outcome of WAP. The mechanism behind this interaction is unclear; former smokers may have an increased susceptibility to the respiratory effects of cigarette smoke (42) and correspondingly may be more susceptible to the effects of occupational exposures. Alternatively, in current smokers, the effects of ongoing particle and gas exposure (via cigarette smoke) may outweigh the adverse effects of occupational exposures on the large airways. However, it is important to note that the relationship between VGDF exposure and wall area percent remained significant in both current and former smokers, suggesting that current smokers are also susceptible to occupational exposures. Further, it is unknown why a similar interaction was not observed for the outcomes of emphysema and small-airway disease; findings from this study prompt consideration of the mechanisms behind the association between occupational exposures and CT-measured respiratory disease. Larger particles impact in the larger airways (43), and where an airborne exposure will interface with small airways and gas-exchanging regions of the lung is determined by particle dynamics and biochemical properties of gases (44), factors that may differ across occupations and job types. Examination of specific exposures (i.e., dust vs. fume) found in different workplace settings may provide more insight into the relationship between exposures and patterns of disease found on CT scan than the VGDF approach allows.

This study has some limitations. Occupational exposures were defined using a self-reported response to a query about VGDF exposure in the longest job, and may not capture important exposures that may have occurred at jobs other than the one held longest. Detailed lifetime employment and exposure histories were not available for this cohort, precluding analysis incorporating measures of duration and intensity. Self-report of VGDF may also be prone to recall bias, which may be mitigated by use of a job exposure matrix (JEM). In a prior publication in the SPIROMICS cohort,

it was found that the sensitivity and specificity of self-reported exposure to VGDF when compared with risk of occupational exposure as measured by JEM was 70.7% and 73.1%, respectively (4). Furthermore, using self-reported VGDF exposures when evaluating the role of job exposures on COPD morbidity yielded results similar to those when using the JEM as an exposure variable (4, 24), suggesting that the results presented in the current article are a reasonable representation of study participants' occupational exposure risk profiles. Of note, most of existing data on occupational exposures and CT imaging characteristics are largely descriptive, and identifying clinically meaningful differences in CT imaging measurements is difficult. In addition, as part of the SPIROMICS inclusion criteria, we are unable to comment on the relationship between occupational exposures and CT measurements of lung disease in a population of individuals without substantial smoking histories. Further, the current analysis is a cross-sectional study, and whether the relationship between job exposures and CT outcomes changes over time is unknown; additional longitudinal research may help define clinically important thresholds of CT-measured disease.

In summary, in this multicenter study of current and former smokers in the United States, VGDF exposure in the longest job was associated with impairments in three distinct CT phenotypes of emphysema, large airways, and small airways, even when accounting for smoking status. These results suggest that quantitative CT imaging is an important tool in the identification of sub phenotypes and may inform further investigation into subgroups of patients with COPD who may be more susceptible to the deleterious effects of occupational exposures (45, 46). The observed impairments may perhaps serve as an explanation for the myriad of adverse clinical outcomes seen in individuals with a history of occupational exposures. ■

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